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Plik pochodzi z repozytorium Wydziału Chemii Uniwersytetu Wrocławskiego

Comparative study of hydrolytic and electron-driven processes in carboplatin biotransformation.

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Rok wydania

2017

Czasopismo

Journal of Inorganic Biochemistry

Numer woluminu

170

Strony

148-159

DOI

10.1016/j.jinorgbio.2017.02.003

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

The results of computational simulation of reaction courses mimicking the transformation of carboplatin from pro-drug into its active shape, responsible for cytotoxic effect, are reported.Implementing the density functional theory (DFT) calculations and the supermolecular approach, we explored the pathways representing two disparate models of carboplatin bioactivation: (1) based on paradigm of carboplatin aquation, and (2) based on new hypothesis that transformation is controlled by electron-transfer processes. The calculated geometrical and thermodynamic parameters were used for evaluation of pathways. In contrast to carboplatin hydrolysis, representing a typical two stage S_N2 mechanism, the postulated electron-driven reactions proceed under the dissociative electron attachment (DEA) mechanism. The reaction profiles predict endothermic effect in both stages of hydrolytic course and final exothermic effects for electron-driven processes. The most effective are hybrid processes including two-stages: water and subsequent electron impact on transformed carboplatin. The aqua-products, manifesting strong electron-affinity, can be the active form of drug capable to cytotoxic interaction with DNA, not only as alkylating agent but also as electron-acceptor. Concluding, the hybrid transformation of carboplatin is more favourable than hydrolytic.

Słowa kluczowe

Carboplatin transformation, Electron-driven reactions, density functional calculations, Hybrid mechanism, Nonclassical Pt-water interactions

Adres publiczny

http://dx.doi.org/10.1016/j.jinorgbio.2017.02.003

Strona internetowa wydawcy

http://www.elsevier.com

Plik został wygenerowany dnia 2026-11-02 11:38:14
Adres w repozytorium https://old.chem.uni.wroc.pl/pl/repozytorium/H1k0oas.